Division of Case Management:

Post Approval Inspections and Enforcement Actions

CBER 101, March 24, 2004

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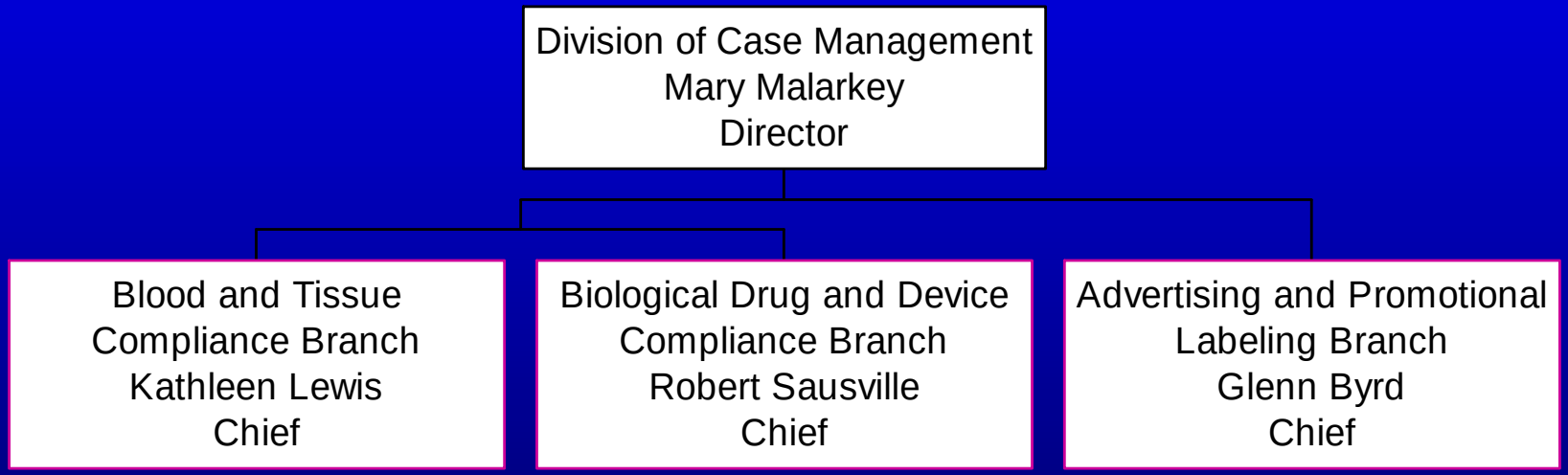
Biological Drug and Device Compliance Branch Division of Case Management,

Office of Compliance and Biologics Quality

DCM Overview

- Organization
- Functions
- Enforcement actions

Organization



BTCB

- Blood and plasma enforcement actions and follow-up (administrative and legal) as defined in Regulatory Procedures Manual
- Tissue enforcement actions and follow-up (administrative and legal)
- Recalls - final determination, HHEs

BDDCB

- Core Team Biologics enforcement actions and follow-up (administrative and legal)
- Other drug and device compliance actions e.g. unapproved products and PLIs/PAIs
- Export/import issues
- Export Certificates
- Compliance Checks

APLB

- Review of advertising and promotional labeling (APL) for approved products and those pending approval
- Internet review (with BDDCB)
- Review of proprietary names for products pending approval
- Review of proposed blood donor incentive programs
- Enforcement actions related to APL
- Review of industry complaints

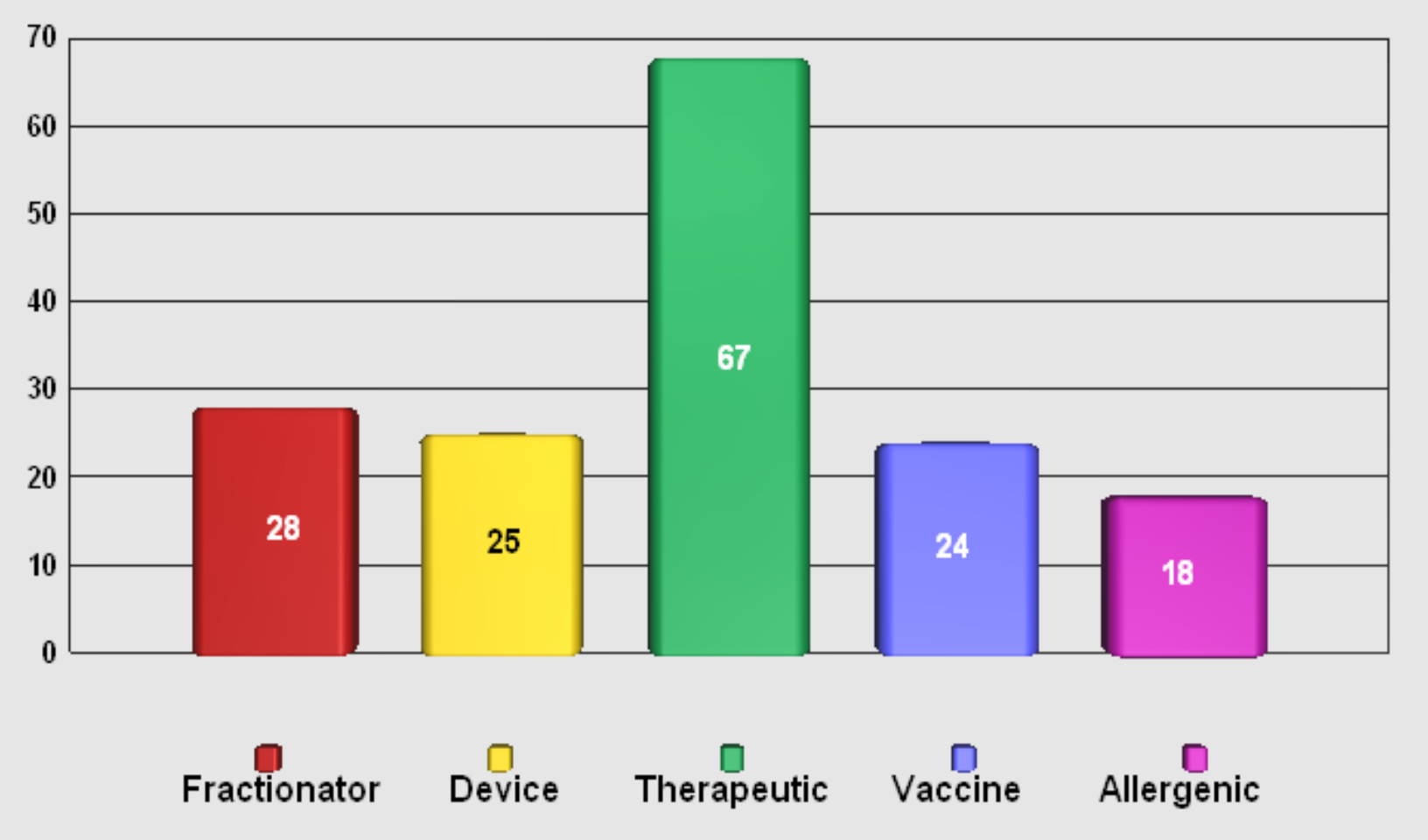
DCM Enforcement Actions

- Warning Letters
- Seizures
- Injunctions
- Notice of Violation – Adv. and promotion
- License Suspension
- License Revocation
  - Notice of Intent to Revoke
- Other – meeting with firm; untitled letter

DCM Enforcement Activities

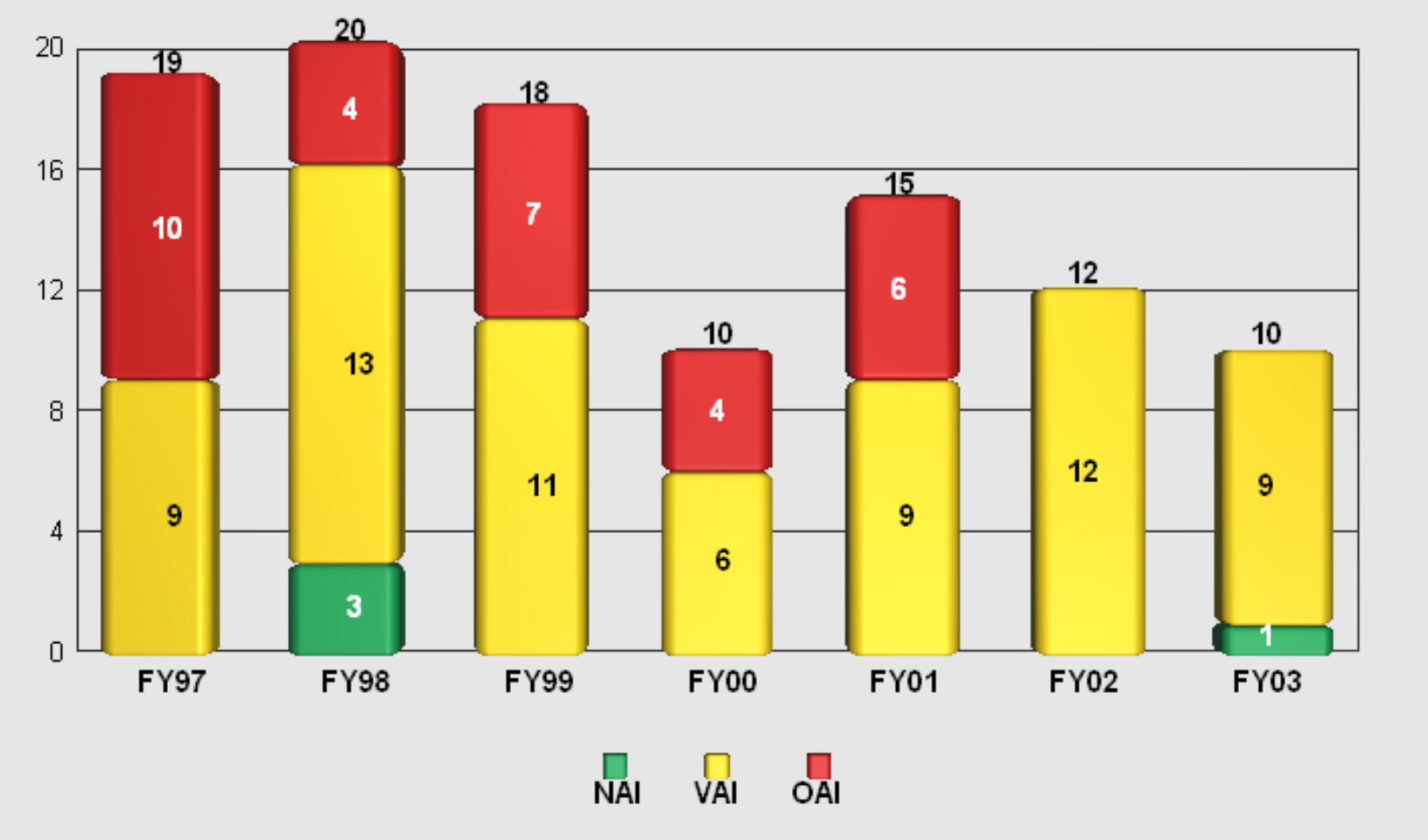
- Blood, Plasma and Tissue
- Team Biologics - Core Team
- Recommendations from FDA district offices
- Unapproved products on internet
- Advertising and Promotional Labeling
  - False and misleading claims

FDA Inspection Inventory*

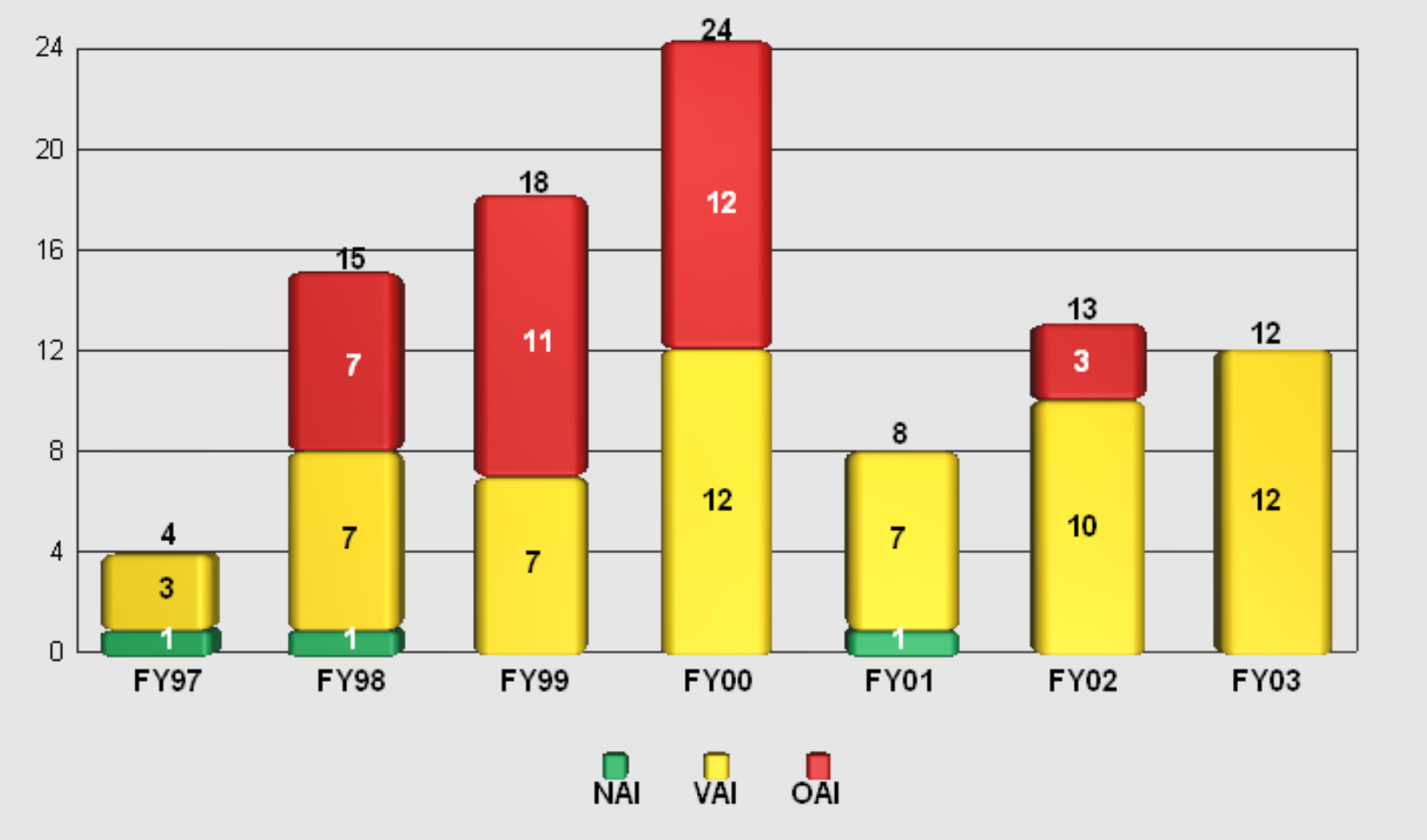


* As of 1/20/04

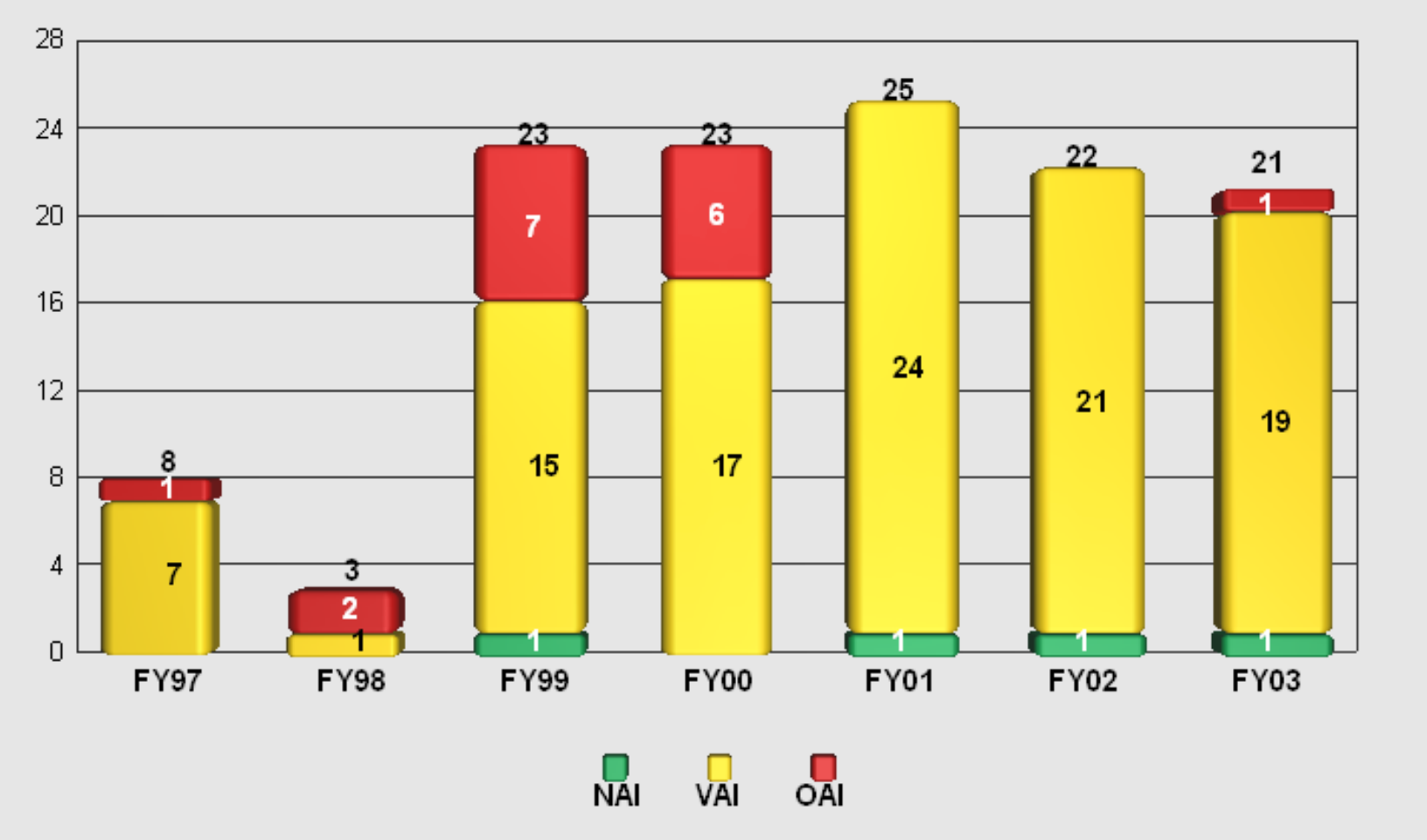
Fractionator Inspection Classifications



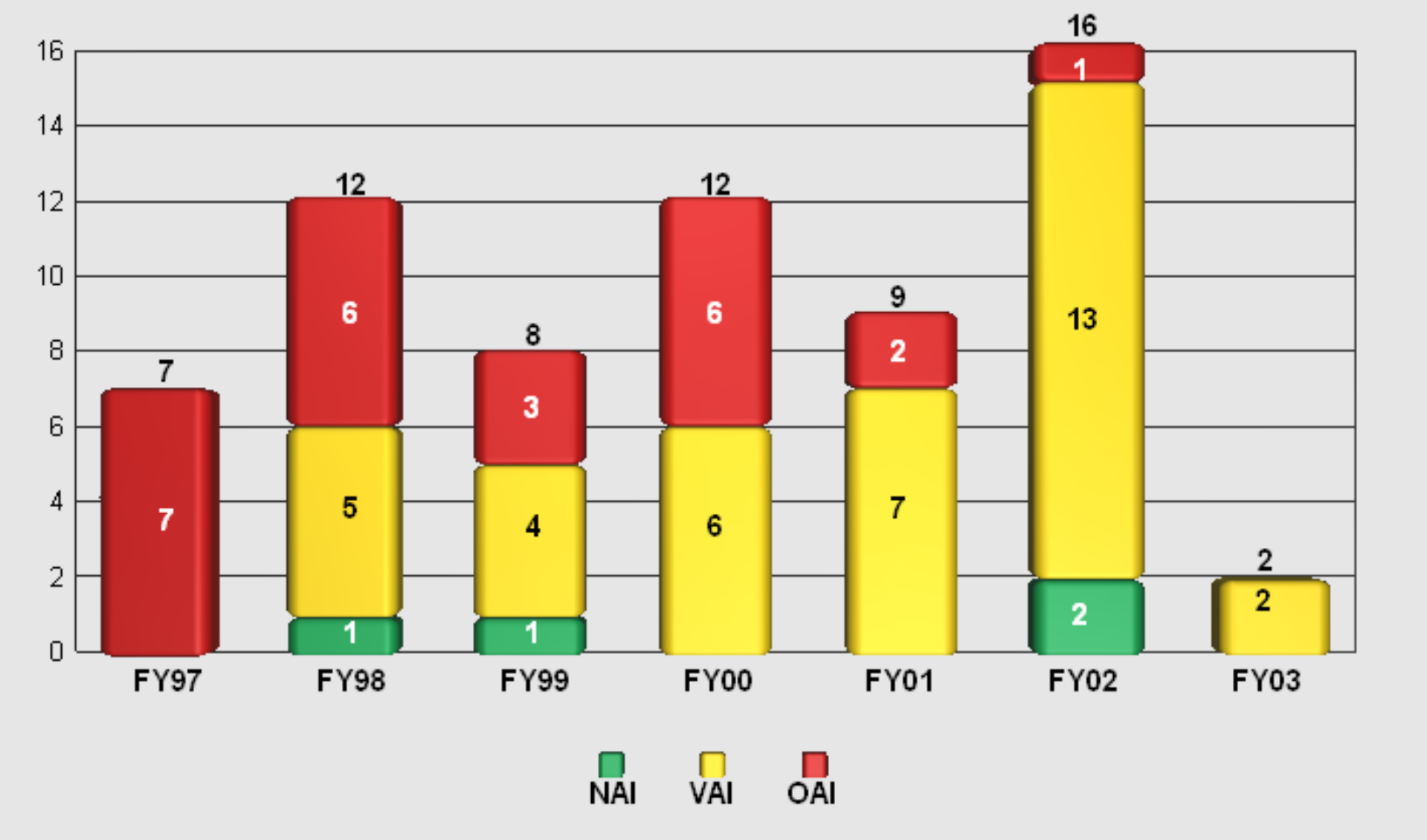
Device Inspection Classifications



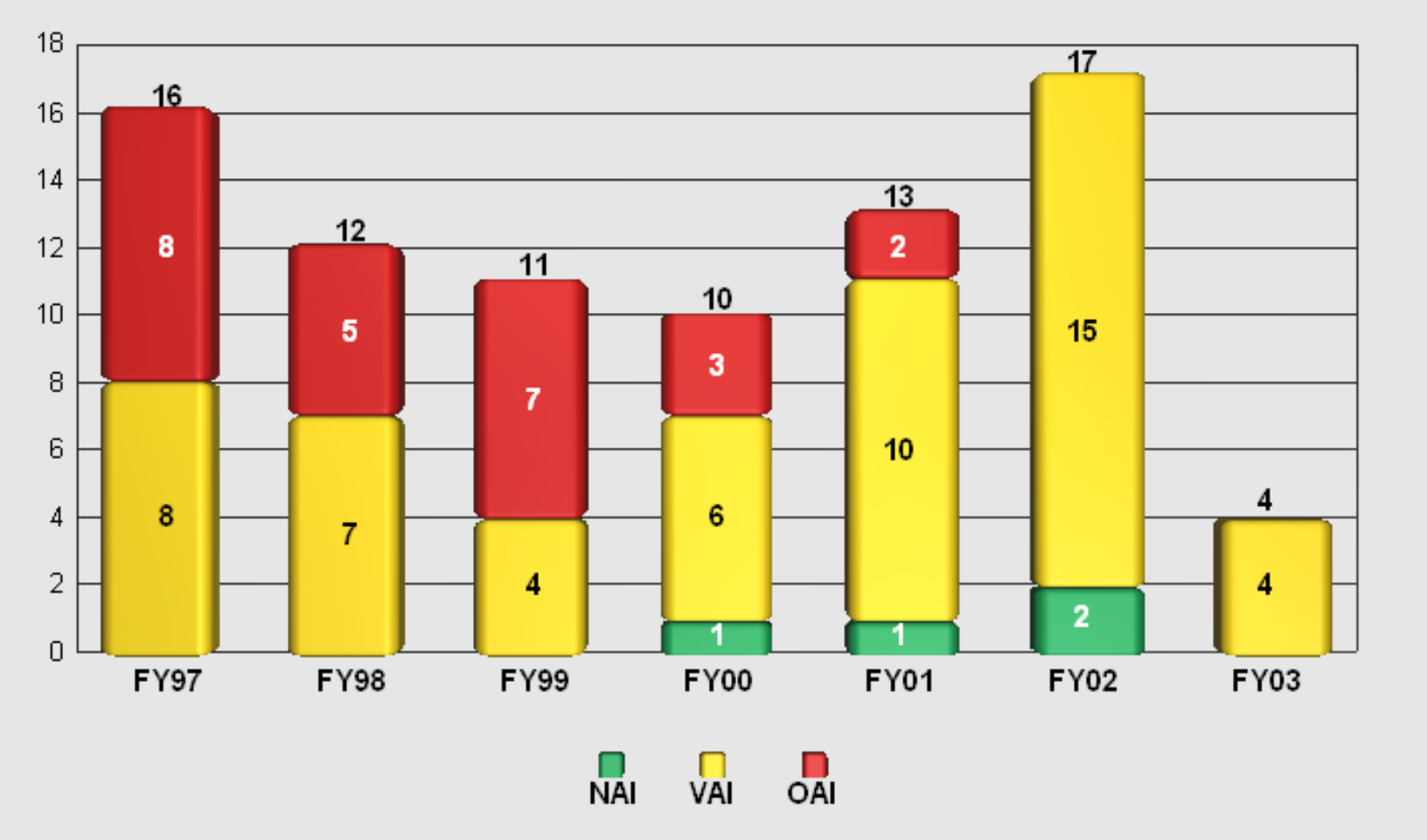
Therapeutic Inspection Classifications



Allergenic Inspection Classifications



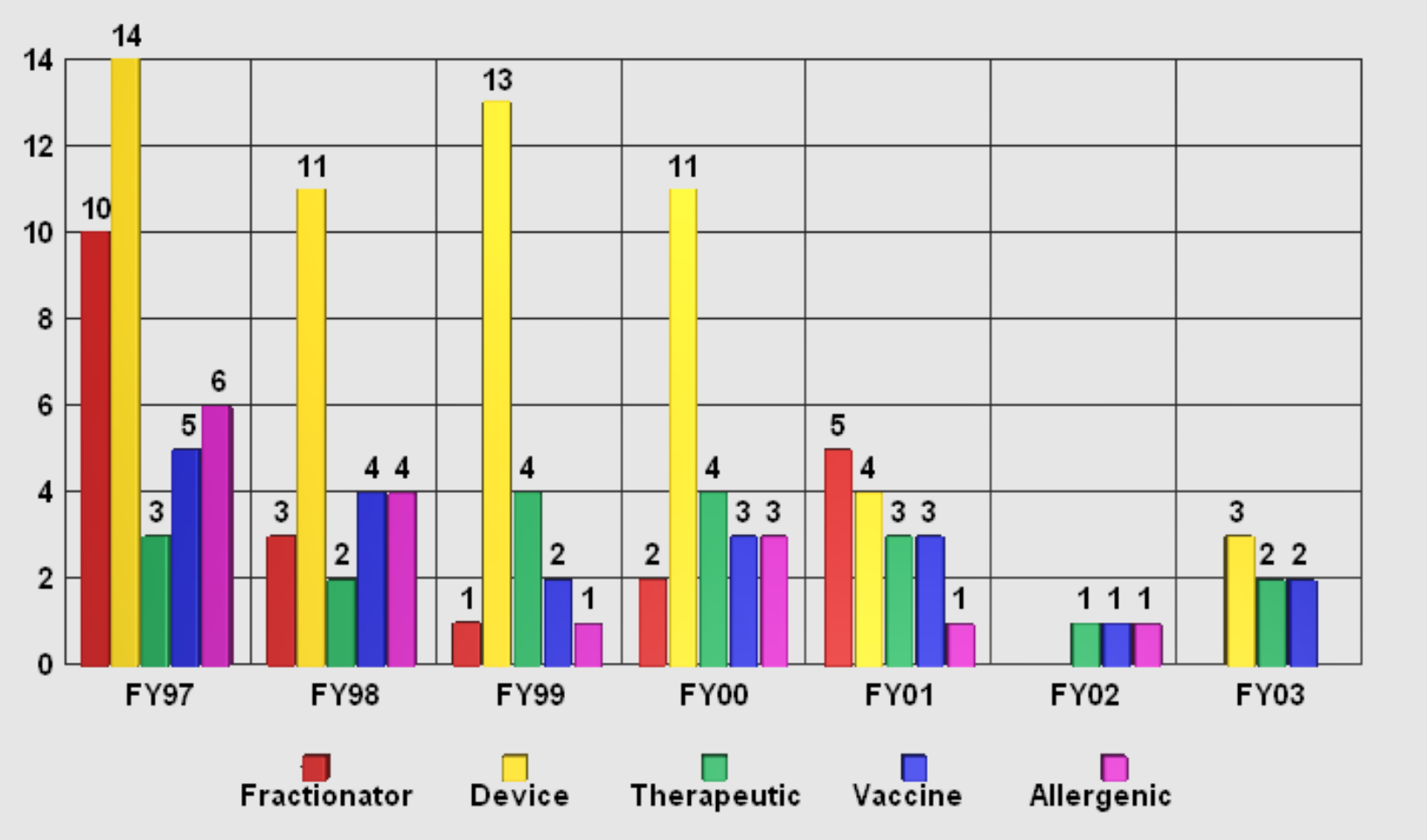
Vaccine
Inspection Classifications



Warning Letters

- Deviations determined to be so significant as to warrant potential enforcement action
- Notification to manufacturer
- Prompt correction

Warning Letters



Warning Letter Citations FY01-03

- Very consistent year-to-year
- May relate to failure to correct root cause

Warning Letter Citations FY01-03
continued

- Failure to implement corrective/preventive action or conduct a thorough investigation
  - 21 CFR 211.192
  - 21 CFR 820.100
- Examples
  - Repeated test failures not investigated
  - Inadequate investigation of failed particulate inspection

Warning Letter Citations FY01-03
continued

- Failure to establish and/or follow adequate written procedures
  - 21 CFR 211.100
- Examples
  - SOPs not followed
  - SOPs inadequate
  - SOPs not established

Warning Letter Citations FY01-03
continued

- Failure to properly test prior to release for distribution
  - 21 CFR 211.165
- Examples
  - Assays used in release-testing not validated
  - Retesting conducted but not addressed in SOP

Warning Letter Citations FY01-03
continued

- Failure to implement adequate production and process controls
  - 21 CFR 820.70
- Examples
  - Routine environmental monitoring not performed
  - Equipment not validated for use

Warning Letter Citations FY01-03
continued

- Failure to implement testing program to assess stability characteristics of product
  - 21 CFR 211.166(a)
- Examples
  - Stability potency tests not completed on schedule
  - Inadequate data to demonstrate sterility of components/product at end of shelf life

License Suspension

- 21 CFR 601.6
- Grounds for revocation exist and danger to health
- Prohibits interstate distribution
- Requires notice to selling agents and distributors with documentation of notice to CBER
- Proceed to revocation, or possibility of resolution
- May be company-wide or site specific

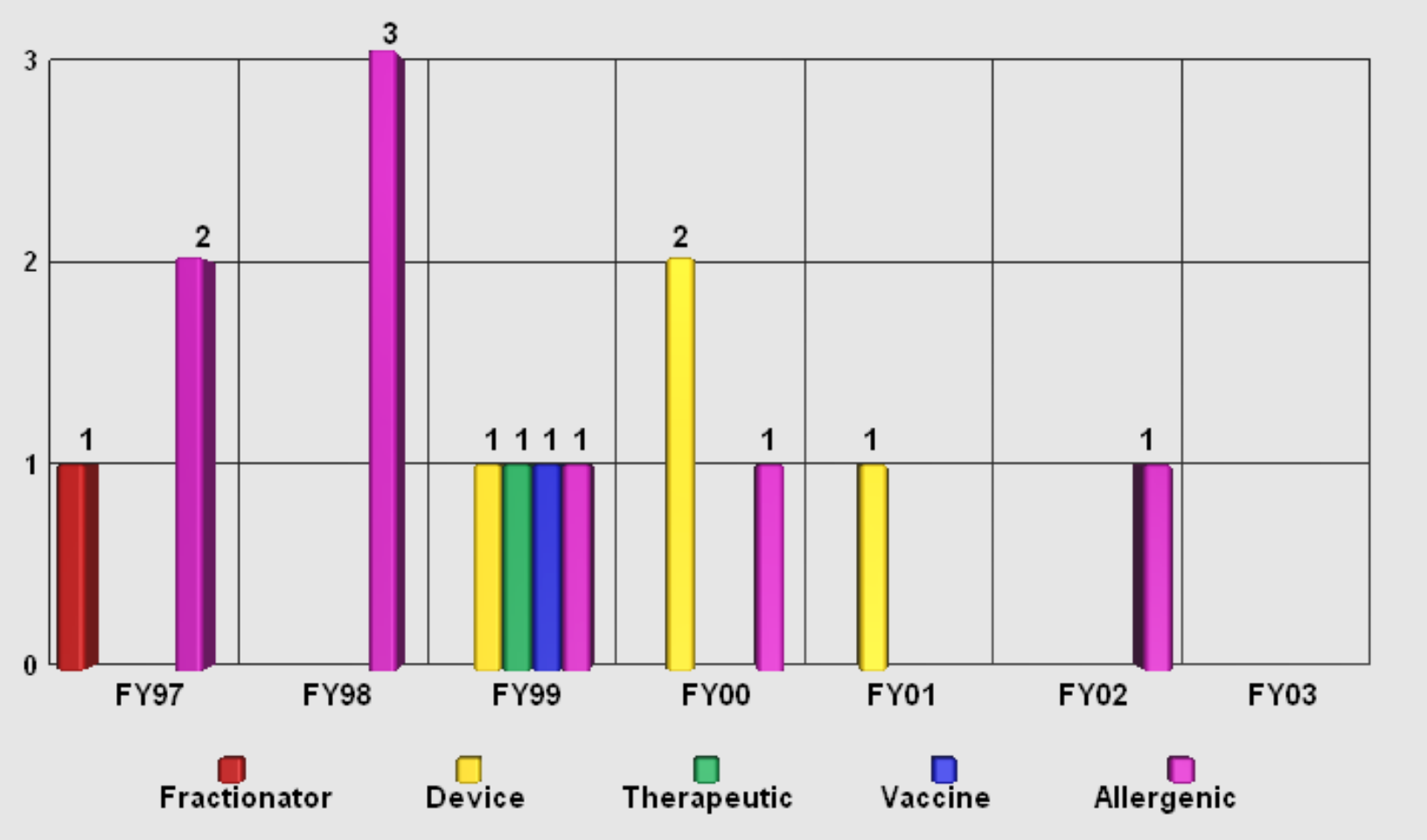
License Revocation

- 21 CFR 601.5
- Discontinuation of manufacturing
  - Manufacturer request for revocation
  - Revocation initiated by FDA
- Failure to report manufacturing change
- CGMP deficiencies
- New method of manufacturing
- Product not safe and effective for intended use(s)/misbranded
- May request hearing

Types of Revocation

- Notice of Intent to Revoke
  - Continuing, significant deficiencies
  - Prior warnings
  - Opportunity to correct and achieve compliance ("reasonable period")
  - If compliance not demonstrated, notice of opportunity for hearing (unless waived)
- Direct Revocation
  - In cases involving willfulness, FDA will proceed directly to revocation
  - No further opportunity to demonstrate compliance

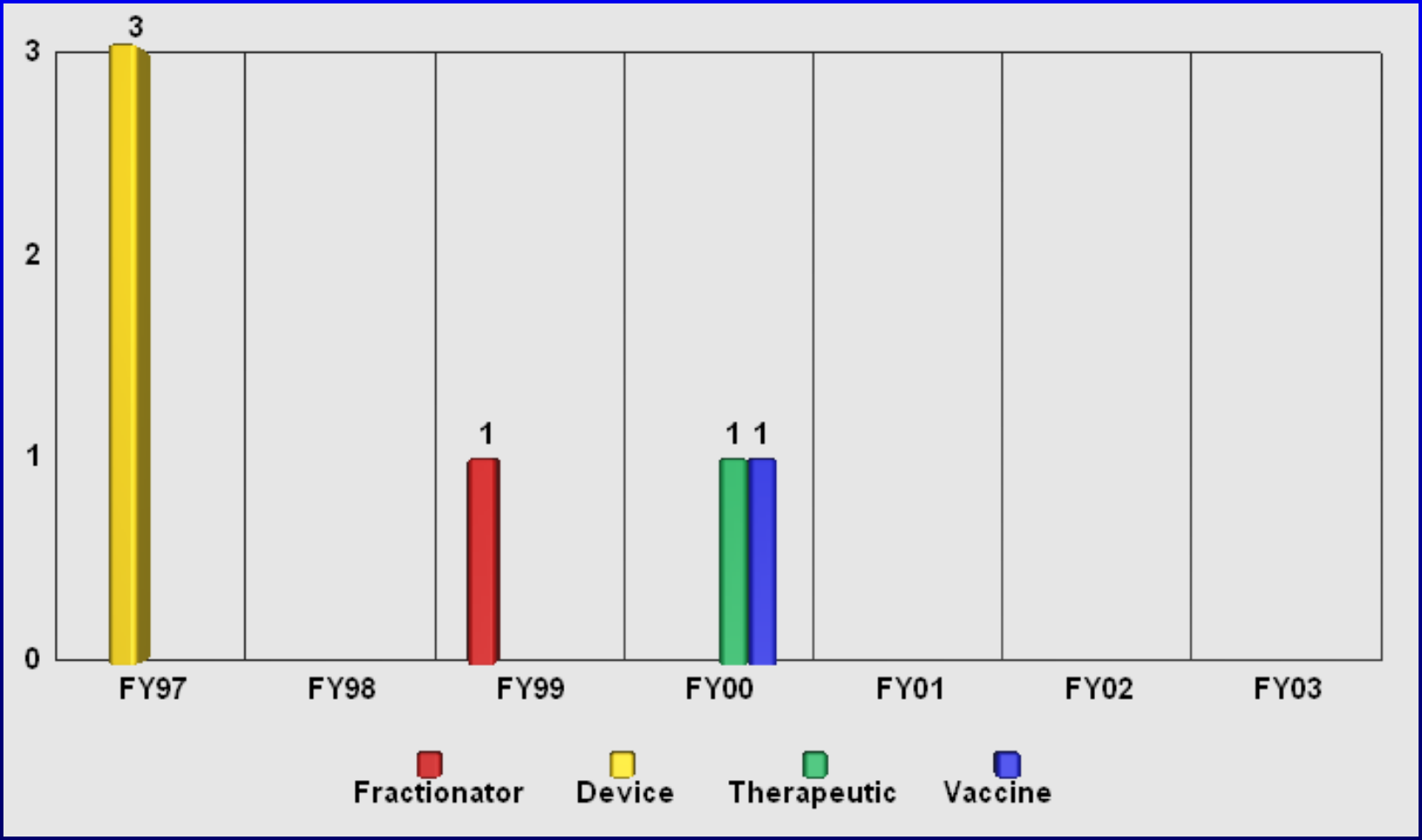
License Suspension/Revocation Notice of Intent to Revoke



Seizures

- Removes product from market
- Not often used for blood/plasma products due to short expiration dates, industry recognition of risk, recall procedures, etc.

Seizures


3
2
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FY97
FY98
FY99
FY00
FY01
FY02
FY03
Fractionator
Device
Therapeutic
Vaccine

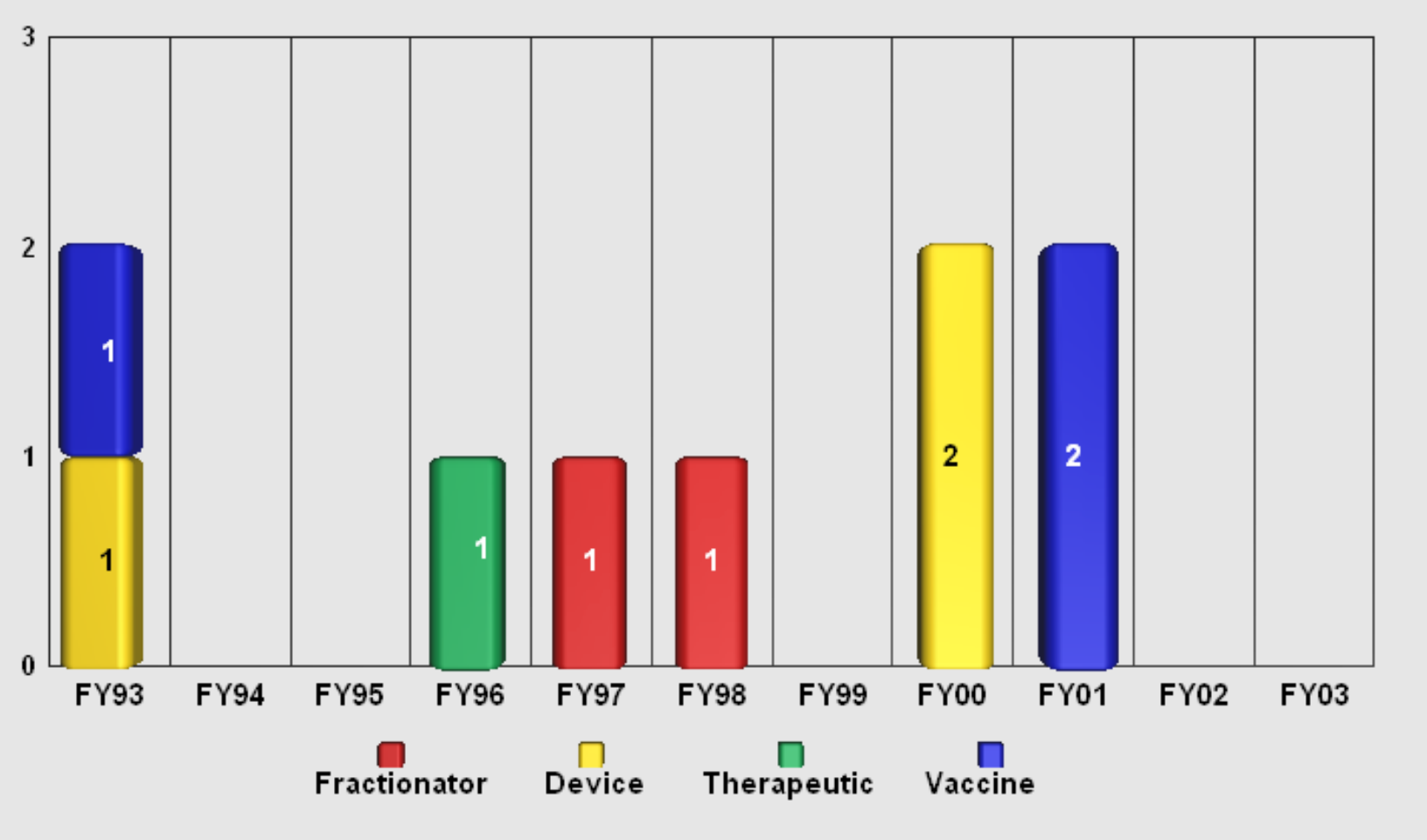
Injunction

- To stop or prevent actions that lead to violation of the law
  - e.g., manufacturing practices that may lead to the introduction of violative products into interstate commerce
- To correct the conditions that caused the violation to occur
- An order issued by the Court in which one or more defendant is ordered to do and/or refrain from doing a specified act or acts

Reasons for Injunction

- Significant out-of-compliance circumstances
  - Repeated violations
  - Types of violations (e.g., system-wide problems)
- Does not preclude additional or concurrent action
  - Recall
  - Public information
  - Seizure
  - License suspension/revocation
  - Criminal prosecution

Injunctions

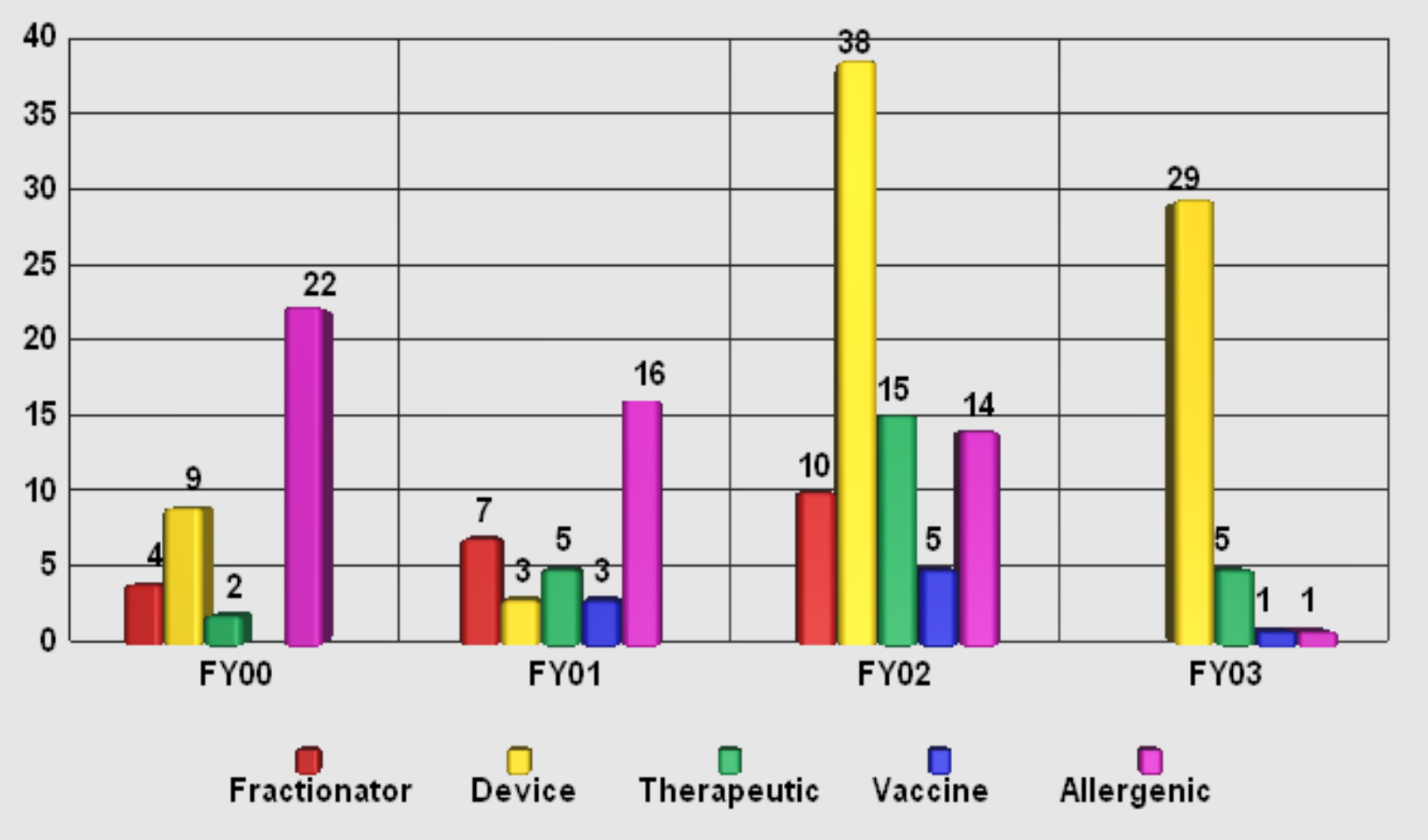


Recalls

- 21 CFR Part 7 Subpart C
- Voluntary action in lieu of FDA-initiated court action for product removal or correction
- Voluntary action to carry out firm's responsibility to protect the public health with respect to its products
- Classified as Class I, Class II, or Class III

Recalls Classified

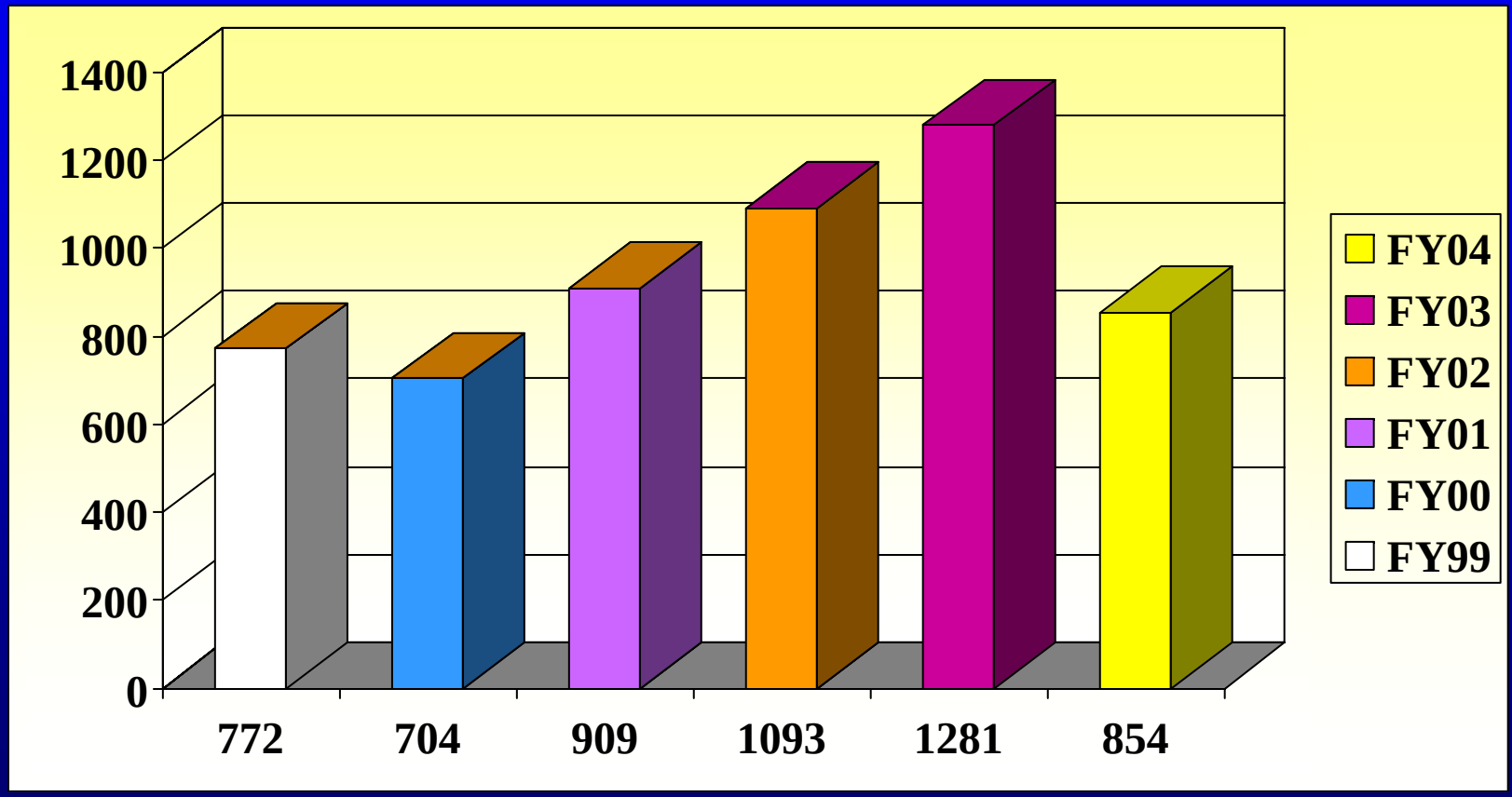
Non-Blood



Compliance Checks

- Performed prior to approval of biologics license applications and major supplements.
- Determination of compliance status of:
  - license holder or potential license holder
  - all manufacturing locations.

Compliance Checks



Summary

- DCM's responsibilities
  - Enforcement actions for CBER regulated products
    - CBER initiated
    - CBER concurred
  - Advertising and promotional labeling review
  - Recalls
  - Compliance checks
  - Export/import

More Information

- CBER External Web site:
  - www.fda.gov/cber
- Division of Case Management
  - 301-827-6201